



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

- 4 Nemes E, Geldenhuys H, Rozot V, et al. Prevention of *M. tuberculosis* infection with H4:IC31 vaccine or BCG revaccination. *N Engl J Med* 2018; **379**: 138–49.
- 5 Arts RJW, Moorlag S, Novakovic B, et al. BCG vaccination protects against experimental viral infection in humans through the induction of cytokines associated with trained immunity. *Cell Host Microbe* 2018; **23**: 89–100.e5.
- 6 Old LJ, Benacerraf B, Clarke DA, Carswell EA, Stockert E. The role of the reticuloendothelial system in the host reaction to neoplasia. *Cancer Res* 1961; **21**: 1281–300.
- 7 Floc'h F, Werner GH. Increased resistance to virus infections of mice inoculated with BCG (*Bacillus Calmette-Guérin*). *Ann Immunol* 1976; **127**: 173–86.
- 8 Netea MG, Dominguez-Andres J, Barreiro LB, et al. Defining trained immunity and its role in health and disease. *Nat Rev Immunol* 2020; published online March 4. DOI:10.1038/s41577-020-0285-6.
- 9 Ritz N, Hanekom WA, Robins-Browne R, Britton WJ, Curtis N. Influence of BCG vaccine strain on the immune response and protection against tuberculosis. *FEMS Microbiol Rev* 2008; **32**: 821–41.
- 10 WHO. Bacille Calmette-Guérin (BCG) vaccination and COVID-19. April 12, 2020. [https://www.who.int/news-room/commentaries/detail/bacille-calmette-gu%C3%A9rin-\(bcg\)-vaccination-and-covid-19](https://www.who.int/news-room/commentaries/detail/bacille-calmette-gu%C3%A9rin-(bcg)-vaccination-and-covid-19) (accessed April 29, 2020).
- 11 Faust L, Huddart S, MacLean E, Svadzian A. Universal BCG vaccination and protection against COVID-19: critique of an ecological study. April 1, 2020. <https://naturemicrobiologycommunity.nature.com/users/36050-emily-maclean/posts/64892-universal-bcg-vaccination-and-protection-against-covid-19-critique-of-an-ecological-study> (accessed April 5, 2020).



Acute limb ischaemia in two young, non-atherosclerotic patients with COVID-19

Coronavirus disease 2019 (COVID-19) was announced a pandemic by WHO on March 11, 2020.¹ As of May 3, 2020, Italy is one of the countries hit hardest by the COVID-19 pandemic, with 28 884 confirmed deaths.² In addition to pulmonary insufficiency, COVID-19 is associated with other life-threatening complications such as sepsis, heart failure, and pulmonary embolism.^{3,4} Here we describe patients with COVID-19 who presented with acute limb ischaemia but did not have atherosclerosis, atrial fibrillation, or pre-existing blood clotting disorders.

Our tertiary care hospital in Parma, Italy, has largely been repurposed to care for patients with COVID-19, reaching more than 800 hospital beds dedicated to patients with COVID-19 at the peak of the pandemic. Within 1 week, we provided care for four patients with COVID-19 with acute limb ischaemia.

Two of these patients had comorbidities (a previous subclavian artery stenting, and a concomitant atrial fibrillation). However, the other two patients with confirmed COVID-19 pneumonia were young and active patients with no comorbidity. At presentation, both patients without comorbidities were receiving low-molecular-weight heparin prophylaxis, and D-dimer concentrations were higher than 9000 ng/mL. One patient, a man aged 53 years who received invasive mechanical ventilation, presented with bilateral lower limb ischaemia secondary to acute aortoiliac thrombosis. He underwent emergent thromboembolectomy through femoral cutdowns, with bilateral pedal pulse recovery. Inspected arteries were free from macroscopic atherosclerotic disease. However, thrombosis reoccurred approximately 2 h after the thromboembolectomy, and the patient died on post-operative day 2. The other patient, a man aged 37 years, received oxygen support through a nasal cannula and presented with an acute ischaemia of the upper left limb. The clot was visible by duplex ultrasound at the level of the humeral artery bifurcation. After 2 days of unfractionated heparin administration, the acute limb ischaemia resolved.

Changes in blood coagulation during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (ie, increased values of D-dimer, fibrin or fibrinogen degradation products, and fibrinogen; decreased antithrombin values, prothrombin time activity, and

thrombin time) have been described by Han and colleagues.⁵ Systemic proinflammatory cytokine response is a mediator of atherosclerosis by inducing the expression of procoagulant factors, local inflammation, and haemodynamic alterations.³ Finally, the receptor for SARS-CoV-2 (angiotensin-converting enzyme 2) is expressed on the membrane of vascular muscle and endothelial cells.³

In view of the young and seemingly healthy patients who develop severe vascular complications during SARS-CoV-2 infection, a prospective registry should be established to aid an understanding of the prevalence and risk factors of acute limb ischaemia in patients with COVID-19, with the aim of defining prophylactic and therapeutic protocols.

We declare no competing interests.

*Paolo Perini, Bilal Nabulsi, Claudio Bianchini Massoni, Matteo Azzarone, Antonio Freyrie
p.perini@live.com

Vascular Surgery, Department of Medicine and Surgery, University of Parma, Parma, Italy (PP, MA, AF); and Vascular Surgery, Cardio-Thoracic and Vascular Department, University Hospital of Parma, Parma 43126, Italy (PP, BN, CBM)

- 1 WHO. WHO Director-General's opening remarks at the media briefing on COVID-19—11 March 2020. <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020> (accessed March 24, 2020).
- 2 Johns Hopkins University. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University. <https://coronavirus.jhu.edu/map.html> (accessed May 3, 2020).
- 3 Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395**: 1054–62.
- 4 Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020; published online March 13, 2020. DOI:10.1001/jamainternmed.2020.0994.
- 5 Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med* 2020; published online March 16. DOI:10.1515/cclm-2020-0188.

Published Online
 May 5, 2020
[https://doi.org/10.1016/S0140-6736\(20\)31051-5](https://doi.org/10.1016/S0140-6736(20)31051-5)